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APPLICATION NO.	FILING DATE.	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,476	06/29/2004	Ryan Thomas Backer	X-15476	9111

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EXAMINER	
BERNHARDT, EMILY B	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/500,476	BACKER ET AL.	
	Examiner	Art Unit	
	Emily Bernhardt	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20-25 and 27-47* is/are pending in the application.

4a) Of the above claim(s) *28,40-43 and 45-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,20-25,27,29-39 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-18,20-25,27,29-39 and 44, drawn to compounds, simple compositions, 1st recited use and process of making of formula I where y=1.

Group II, claim(s) 1-18,20-25,27,30-39 and 44, drawn to compounds, simple compositions, 1st recited use and process of making of formula I where y=2.

Group III, claim(s) 28, drawn to complex compositions employing compounds of I or II and additional active ingredients.

Group IV, claim(s) 40-43, drawn to additional process of making compounds of I-II.

Group V, claim(s) 45-47, drawn to additional uses for I-II.

If Group III is elected applicants are required to elect a compound group (i.e. one of I-II) and a single species from this group and one type of additional active ingredient and a species embracive of this class of ingredient. If IV or V a specific use or single process must be chosen along with a compound group.

The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack

the same or corresponding special technical features for the following reasons: Compounds of Groups I-II relate to compounds of considerable structural dissimilarity in view of the varying E,T choices as well as substituted derivatives thereof. The mandatory structural feature common to all of the groups, namely the carboxamido sidechain, cannot be considered a patentable advance over the art given that said feature is old as evidenced by the art cited in applicants' PCT Search Report as well as art cited below. Where more than one use and process of making exists only the first recited use/process is considered to form part of the main invention. See 37 CFR 1.475(d). Group V lacks unity with remaining groups as it recites multiple combinations which are not art-recognized equivalents of each other for a variety of intended uses.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement

between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

During a telephone conversation with Mr. Myers on 9/19/06 a provisional election was made with right of traverse to prosecute the invention of I, claims 1-18,20-25,27,29-39 and 44. Affirmation of this election must be made by applicant in replying to this Office action. Claims 28,40-43 and 45-47 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 1-18,20-25,27,30-39 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Is R8 as "oxo" really intended as such a group would exceed valency requirements for N and O atoms which can be attached to said variable. See the many variables which include R8 in the choices.

2. Claim 9 recites for "R" as being hydrogen which is not technically correct since H is only present when p=0 not 1. Clarification is needed.

3.In claim 31 note the misspelling "boromo". Also is the reactant limited to 2-bromobenzaldehye *per se* or to all 2-Br containing aldehydes? Note that an additional variable "R" is also present in the aldehyde formula.

4. In claim 39 "formula (4)" is not present in step (e) so applicants' intent is not clear. It would appear that formula (6) should be recited and deprotecting when necessary would afford compounds of formula 1.

Claims 9,14 and 15 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Each of these claims recite subject matter outside the scope of

claim 1. In claim 9 it is not seen where the phenyl/benzyl groups in R can be substituted with halo or hydroxyl. In claim 14 haloalkyl and (D)C(O)C1-C8alkyl are not in claim 1 and in claim 15 benzyloxy is not seen to be within the ambit of R3 in claim 1.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 9, 14 and 15 are rejected under 35 U.S.C. 101 because it contains subject matter that lacks a utilty. As discussed in the above par. four rejection, there are moieties recited that are outside the scope of main claim 1 as well as not included within the generic teachings of the specification .Thus said subject matter cannot be ascribed the utilities disclosed for members within the scope of the instant invention.

Claims 1-18, 20-25,27,29-39 and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. **The following reasons apply.**

1.All the Claims which embrace any solvate are nonenabled since generally not all solvents can form solvates with all compounds. There is no process enabling such a scope in the specification .

Note Vippagunta provided in parent and cited by applicants herein who flatly states on p.18, section 3.4 the following: "Predicting the formation of solvates or hydrates of a compound.... Is complex and difficult." Applicants' own specification confirms this since despite numerous examples presented none of the final products were obtained as solvates.

2. Scope of prodrugs appearing in claim 29 is not enabled. A prodrug is chosen based on some undesirable property present in the parent compound and once the type of improvement is identified there is testing to determine the prodrug's efficacy and ability to regenerate the parent compound. It is not the norm that one can predict with any degree of accuracy a particular prodrug form of an active compound will be more soluble, more easily handled in formulations or more bioavailable without actual testing *in vivo* . Thus the design of prodrugs is far from trivial and is dependent on the undesirable properties of the active compound(s) which will vary from drug to drug. Thus in the absence of any guidelines (none is seen in the specification) as to what type of prodrugs are suitable for instant compounds and at which location in the species of claim 29 more than undue

experimentation is required to practice the invention.

3.Specification is not adequately enabled for the scope of piperazines claimed which can have a variety of heterocyclic/heteroaryl groups within substituents in R1a, R1b, R and R8. From a reading of the specification such rings include not only monocyclics but also fused systems both saturated, partially unsaturated and heteroaromatics which in turn can be further substituted although intended substituents are not set forth. Compounds made and some tested in an assay for MC4 receptor binding are always 4-Cl phenyl as R3 with T rings as hydrogenated isoquinolines and isoindoles with alkyl,acyl, haloalkyl substitution thereon. Thus, there is no reasonable assurance as to what other substituents will work given the limited test data test data reported on p.68 and thus no structure-activity trends that can be evaluated. Receptor binding is known to be structure-sensitive in general. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art. Also note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a),August 2000 edition which considers such factors as:

1) Breadth of the claims- the scope easily totals in the millions if not billions;

2) Level of unpredictability in the art – the invention is pharmaceutical in nature involving inhibitory activity at a particular receptor (melanocortin-4). It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be unpredictable. See In re Fisher 166 USPQ 18;

3) Direction or guidance- as stated above no heterocyclic-substituted compounds at any one location have been made much less tested ;

4) State of the prior art- there are no piperazines of similar structure having such a range of functional groups that are known for possessing the activities asserted herein and thus the state of the prior art would also not support such a scope. Note Dyck applied below is directed to a small portion of applicants' invention;

5) Working examples- test data has been presented for a very homogeneous group of compounds and thus no clear evaluation of which hetero rings at various positions out of the many claimed might affect potency to a large or small degree.

In view of the above considerations, this rejection is being applied.

Claim 44 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating obesity, does not reasonably provide enablement for **preventing the onset of this eating disorder**. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The current state of the art does not reflect that MC-4 receptor agonists can prevent weight gain but rather is directed to evidence showing a reduction of food intake in obese animals. See for example Sebhat and Campfield. Copies of these references can be found in copending case 10/466249.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6,8,8,12-18,20,22,25,27 and 44 are rejected under 35 U.S.C. 102(e) as being anticipated by Dyck (WO'410). Dyck describes several compounds within the instant scope for the same use and mechanism of action as being claimed herein. See examples such as 2-4,6,7,9,17 and 23-9 which correspond to instant "T" ring as tetrahydroisoquinoline . Dyck is applied as of its US provisional filing date of 10/09/01 which precedes applicants' US provisional

filing date. A review of said provisional application shows pertinent species described therein.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dyck. Claim 10 requires certain R^{1a} choices including the last choice which is taught by Dyck as a choice for R6 therein. See p.8 in Dyck for a list of R6 choices which includes the last choice in claim 10. The last species of claim 29 is also an obvious variant since aminoalkyl as a R6 choice is also taught in Dyck which permits this group to be attached to the cycloalkyl ring by way of an alkylene link. Cyclopentane is clearly contemplated as well. See p.9 in the alkanediyl definition. Thus it would have been obvious to one skilled in the art at the time the invention was made to expect compounds claimed herein that are modified at instant R^{1a} and vary in the size of the cycloalkane to also possess the uses taught by the art in view of the equivalency teachings outlined above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

E Bernhardt

Emily Bernhardt
Primary Examiner
Art Unit 1624